IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Thorsten Heinzel	Examiner: AEDER, SEAN E
Serial No.: 10/528,104	Group Art Unit: 1642
Filed: SEPTEMBER 28, 2005	Confirmation Number: 3483

Title: **USE OF MOLECULAR MARKERS FOR THE PRECLINICAL AND CLINICAL PROFILING OF INHIBITORS OF ENZYMES HAVING HISTONE DEACETYLASE ACTIVITY**

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Non-Compliance mailed March 9, 2010, in response to Appellants' Brief on Appeal filed June 30, 2008, please consider the following:

An amended Section (V) "Summary of Claimed Subject Matter" is enclosed herewith

Please replace the previously-filed Summary of Claimed Subject Matter section of the Appeal Brief with the following:

(V) SUMMARY OF CLAIMED SUBJECT MATTER

One embodiment of Appellants' invention (**independent claim 1**) is directed to a method for the characterization of a histone deacetylase (HDAC) inhibitor or a potential HDAC inhibitor, wherein said HDAC inhibitor or potential HDAC inhibitor is a molecule which inhibits the enzymatic activity of said HDAC, comprising determining in a sample the amount of a molecular marker which is HDAC protein, wherein the sample is derived from cells which have been treated with said HDAC inhibitor or potential HDAC inhibitor, and wherein a change in the level(s) of said molecular marker in the presence of said HDAC inhibitor compared to the level of said molecular marker in the absence of said HDAC inhibitor indicates that said test compound is an HDAC inhibitor or a potential HDAC inhibitor. See, for example, page 5, paragraphs 2–4 of the originally-filed specification. See also, the paragraph bridging pages 12 and 13 of the originally-filed specification (for "enzymatic activity") and page 1, ¶1 and page 2, lines 3–5 of the originally-filed specification.

Claims 2–4, 6–10, 14 and 28 are either directly or indirectly dependent on independent claim 1. Dependent **claim 2** recites that the the molecular marker is HDAC-2 protein (see, page 5, ¶3; under the "RESULTS" section of page 22; and the disclosure contained in, for example, Fig. 10 for support**). Claim 3** recites that the sample is derived from a tissue affected by a disorder. See, page 6, lines 17–18. **Claim 4**, which is dependent on claim 3, recites that the disorder is skin cancer, melanoma, estrogen receptor-dependent and independent breast cancer, ovarian cancer, prostate cancer, renal cancer, colon and colorectal cancer, pancreatic cancer, head and neck cancer, small cell and non-small cell lung carcinoma, leukemias and other types of blood cell cancer or an endocrine disease based on aberrant recruitment of histone deacetylase. See, for example, page 6, last paragraph and page 7, ¶1 of the originally-filed specification. **Claim 6** recites a method of detection of the molecular marker using antibody molecules. See, page 8, ¶1. **Claim 7**, which depends on claim 6, recites methods for antibody-based detection of such markers, such as, for example, Western Blotting, ELISA, immunohistochemistry and/or flow cytometry. See, for example, the paragraphs bridging page 8, last paragraph to page 9, ¶3 of the originally-filed specification. **Claim 8** recites an additional element of selecting an inhibitor based on the modulation of the expression of the molecular marker. See, for example, page 10, lines 6–10. **Claim 9** recites the use of a reference sample, wherein the reference sample is derived from cells which have not been treated with said HDAC inhibitor or potential HDAC inhibitor. See, for example, page 10, lines 16–19. **Claim 28** is

supported, at least, by the disclosure contained in page 1, ¶1 and page 2, lines 3–5 of the originally-filed specification (i.e., "enzymes having histone deacetylase activity" carry out "removal of acetyl groups").

Another embodiment of Appellants' invention (independent **claim 10**) relates to a method for profiling histone deacetylase (HDAC) inhibitors or potential HDAC inhibitors, comprising contacting a cell with an HDAC inhibitor or potential HDAC inhibitor; determining the amount of a molecular marker which is HDAC protein in the presence and absence of said inhibitor; and creating a profile of said HDAC inhibitor or potential HDAC inhibitor based on its ability to down-regulate the expression of said molecular marker which is HDAC protein. See, for example, page 11, 1st paragraph and page 13, ¶3 (lines 12–14 at page 13) of the originally-filed specification. **Claim 14** directly depends on independent claim 10. **Claim 14** is directed to the use of antibody molecules directed against HDAC-2 protein. See, page 8, ¶1 and the disclosure contained in Example 2.

Yet another embodiment of Appellants' invention (**independent claim 22**) is drawn to a method for the characterization of a histone deacetylase (HDAC) inhibitor or a potential HDAC inhibitor, comprising contacting a cell with a test compound and measuring the level(s) of a molecular marker which is HDAC protein, wherein a reduction in the level(s) of said molecular marker in the presence of said HDAC inhibitor compared to the level of said molecular marker in the absence of said HDAC inhibitor indicates that said test compound is an HDAC inhibitor or a potential HDAC inhibitor. Support for claim 22 can be found in, for example, the disclosure contained in Example 2 of the originally-filed specification. See also the disclosure in Figs. 6-10 and the description thereof in the "Methods" and "Results" sections of Example 2. In one such study, F9 teratocarcinoma cells or HEK293T cells were exposed to (i.e., *contacted with*) VPA and other potential HDAC inhibitors (e.g., TSA, TPX, MS-275) and levels of HDAC-2 and HDAC-1 or HDAC-3 (control) were determined by Western blot analysis. The HDAC-2 expression level in VPA-treated cells was *compared to untreated cells* (see, Fig. 6B and 6C). It can be seen that compared to control (i.e., untreated) cells, a 36-hour treatment with VPA at 1 mM (F9 cells) or 10 mM (293T cells) *completely abolished* HDAC-2 expression (i.e., a dose-dependent reduction was observed). In summary, the specification expressly teaches that "the present invention demonstrates the ability of *certain* HDAC inhibitors, in particular valproic acid, to *selectively induce degradation of the HDAC-2 protein* additionally to their HDAC inhibitory activity. This selective reduction in HDAC-2 protein levels is seen after stimulation with valproic acid and butyric acid but not with other HDAC inhibitors such as trichostatin A, trapoxin, and MS-275. Thus, HDAC inhibitors such as valproic acid inactivate HDAC-2 through two different mode of actions: they inhibit HDAC-2 activity and induce

proteasomal degradation. The measurement of these combined activities may serve *as a profiling tool for the identification of novel, and potentially more potent, inhibitors of enzymes having HDAC activity*."

REMARKS

Non-compliant Brief

Appellants respectfully traverse the contention that the Brief on Appeal submitted on October 30, 2008 is non-compliant for failing to provide a summary of the subject matter of claim 28. In particular, the last paragraph at page 3 of the Appeal Brief provides a concise explanation of the subject matter of claim 28 and points to Example 2 of the original-specification for support. However, purely in order to advance prosecution, Applicants submit herewith a new "Summary of the Claimed Subject Matter" section of the Appeal Brief, wherein each and every claim element recited in claim 28 has been outlined in detail and the supporting disclosures in the specification have been identified. Entry thereof is earnestly solicited.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

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